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In response to the submission of an Interregional Research Project Number 4 (IR-4) tolerance petition, the Health Effects Division has updated the hazard characterization for deltamethrin. Modifications from previous risk assessments include endpoint selection, FQPA safety factor and the selection of a dermal endpoint. HED's response to the tolerance petition can be found in a separate risk assessment document for deltamethrin (Response to Tolerance Petition for Use on Flax, D. Dotson, D335134).

Rec'd in RIMUERB 8/19/2009

In support of the tolerance petition for the proposed use on flax, the Health Effects Division (HED) has re-evaluated the toxicology database for deltamethrin. Several changes were made from the previous risk assessment (Memo, D262496, D. Dotson, *et al.* 11/15/2004) including endpoint selection, FQPA safety factor, and selection of a dermal endpoint. A single endpoint of decreased motor activity from an acute oral literature study (Wolansky et al. 2006) is being used for all durations and all exposure scenarios (acute, chronic, dermal, inhalation, and incidental oral). The 10X FQPA safety factor has been retained for children, and applies to all scenarios involving children including acute and chronic dietary, dermal, incidental oral, inhalation, and aggregate assessments. Based on literature studies, children were found to have a diminished capacity to detoxify deltamethrin relative to adults. Deltamethrin has low dermal absorption and low toxicity via the dermal route based on the results of a subchronic dermal study; however, an endpoint for dermal assessment was chosen from an oral study since neurotoxic parameters were not evaluated in the dermal study. The selection of neurotoxicity as an endpoint for risk assessment, along with the observed susceptibility in children, contributed to the inclusion of a dermal endpoint. HED considers the hazard characterization to be highly conservative given that increased susceptibility in children is likely to occur at doses greater than children are expected to encounter in residential settings, and because humans potentially have the ability to detoxify deltamethrin at an accelerated rate relative to the rodent model.

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1.0 Hazard and Dose-Response Characterization

1.1 *Database Summary*

1.1.1 Sufficiency of Studies/Data

Based on the proposed use pattern, the toxicology database for deltamethrin is adequate for risk assessment. There are acceptable studies available for endpoint selection that include 1) subchronic oral toxicity studies in rats and dogs; 2) a chronic oral toxicity study in dogs and carcinogenicity studies in rats and mice; 3) developmental and reproduction studies in rats and a developmental study in rabbits; 4) acute (ACN), subchronic (SCN), and developmental (DNT) neurotoxicity studies in rats and; 5) a subchronic dermal toxicity study in rats. There is also a complete mutagenicity battery, as well as an acceptable metabolism study in the rat. Additionally, several literature studies describing deltamethrin toxicity are available. As part of the new EPA 158 guidelines, an immunotoxicity study in rats and/or mice is required (see Appendix III). However, there were no signs of immunotoxicity in any of the studies. Therefore, an additional 10X database uncertainty factor (UF_{DB}) is not needed to account for the lack of the required immunotoxicity study.

1.1.2 Mode of action, metabolism, and toxicokinetic data

Deltamethrin belongs to the pyrethroid class of insecticides. Pyrethroids are synthetic analogs of the natural pyrethrins, the insecticidal components of extracts from the pyrethrum flower (*Chrysanthemum cinerariaefolium*). The pyrethroids modulate nerve axon sodium channels, resulting in neurotoxic effects (Soderlund et al. 2002). There are two subcategories of pyrethroids based on structure, function, and resulting toxicity. Type I pyrethroids lack a cyano group, induce repetitive neuronal firing and result in toxicity signs characterized by fine tremors (T syndrome). Type II pyrethroids contain a cyano group, cause a voltage-dependent block in affected neurons and result in toxicity signs characterized by choreoathetosis (whole-body tremors) and salivation (CS syndrome). This mode of action is applicable to insects and mammals. Deltamethrin is a type II pyrethroid.

The pharmacokinetic properties of pyrethroids are greatly influenced by structure and configuration. Pyrethroids typically contain 2 or 3 chiral centers resulting in several structural isomers. Metabolism of the isomers occurs through 2 competing pathways: hydrolysis for trans-isomers, and oxidation for the cis-isomers. The ramifications of the differential metabolism are further discussed in section 2.3. Many pyrethroids are commercially sold as enrichments of the most efficacious isomers. For instance, permethrin is available as a 40:60 cis:trans mixture and deltamethrin as a >90% cis-isomer product.

1.2 *Toxicological Effects*

<u>*Guideline Studies*</u>

Deltamethrin targets the nervous system. In guideline animal studies, effects in the rat, dog and rabbit primarily included salivation, unsteadiness, convulsions, altered posture, hypersensitivity

to sound and decreased motor activity. Increased duration of dosing did not either significantly lower the NOAEL for the neurotoxic effects or increase the severity of these effects. In fact, neurotoxicity effects were identified in the chronic and subchronic rat within hours to days of initial dosing, but decreased over several weeks. Decreases in body weight and body weight gain were also noted in subchronic, chronic and reproductive studies.

The toxicity of deltamethrin by oral administration was not affected by the use of gavage or dietary administration. Gavage studies, including the acute neurotoxicity study in rats and the prenatal developmental studies in rats and rabbits had similar LOAELs compared to studies using dietary administration (i.e. subchronic, chronic, and reproductive studies). Additionally, there was no evidence of systemic or local effects when deltamethrin was dermally applied in a 21-day study in rats. Low toxicity via the dermal route is most likely due to the low potential for dermal absorption through the skin (approximately 1%).

Deltamethrin did not have any adverse effects on offspring in the prenatal developmental studies in rats and rabbits or in the DNT in the absence of maternal effects. There was increased pup mortality in the reproduction and fertility study in rats. However, the increase in pup deaths was correlated with weaning. The concentration of deltamethrin in maternal milk was not reported. However, reproductive studies involving other pyrethroids have indicated that chemical concentration in milk is far below the levels found in feed. Therefore, as the pups transitioned from milk to feed, their ingestion rate of deltamethrin likely increased, resulting in heightened toxicity. In the case of deltamethrin, elevated toxicity was manifested as increased pup deaths.

There was no evidence of carcinogenicity in the combined chronic/carcinogenicity study in rats or the carcinogenicity study in mice. Deltamethrin is classified as "Not likely to be carcinogenic to humans." In a battery of mutagenicity studies, there was no evidence of a mutagenic effect.

Literature Studies

Deltamethrin has been extensively covered in the open literature. There are numerous studies examining the mode/mechanism of action, pharmacokinetics, neurotoxicity, and developmental neurotoxicity of pyrethroids. Studies most relevant to the deltamethrin risk assessment will be described in the appropriate sections of this document.

1.3 *Dose-Response*

Several deltamethrin guideline studies have been conducted including acute, subchronic, and chronic durations assessing systemic toxicity, neurotoxicity, and developmental and reproductive toxicity. Additionally, there are numerous literature studies describing the toxicology of deltamethrin. However, a single endpoint (motor activity), from an acute oral neurotoxicity study in rats (Wolansky et al. 2006), was chosen for all exposure scenarios and durations.

Motor activity is presently one of the most characterized neurobehavioral endpoints for measuring pyrethroid toxicity (Wolansky and Harrill 2008); it is defined as the summation of locomotor (ambulatory movement) and non-locomotor (i.e., scratching, grooming, or head or body shakes) activities, often measured in a maze setting. Motor activity has been use to define

several characteristics of deltamethrin toxicity in rodents including threshold toxicity, relative potency, and the influence of vehicle and volume on oral gavage dosing.

Although the selected endpoint is from an acute study, it is appropriate for subchronic and chronic studies based on the rapid metabolism and low potential for bioaccumulation. Following an oral dose of deltamethrin, peak effects in rodents are seen within 2 hours, with a full recovery by 24 hours. Furthermore, the plasma half-life of deltamethrin in rodents is less than 16 hours. Therefore, a repeated dose over multiple days is comparable to a series of acute doses. This is corroborated by similar LOAELs in acute and chronic guideline studies.

The LOAEL and NOAEL from Wolansky et al. (2006) were 2.5 mg/kg and 1 mg/kg, respectively, based on reduced activity. Similarly, the subchronic and chronic dog studies have equivalent NOAELs (1mg/kg) based on clinical signs of neurotoxicity. Finally, Wolansky et al. (2006) is a robust study; six dose levels were used ranging from 0.03 to 10 mg/kg demonstrating a clear NOAEL and LOAEL; each dose group consisted of 8 to 18 animals, minimizing variability among the dose groups; and vital study parameters such as gavage vehicle, vehicle volume, and time to peak effect were all chosen to appropriately characterize deltamethrin toxicity. Therefore, the Wolansky et al. (2006) study is appropriate for endpoint selection because it is based on an appropriate measure of toxicity, an appropriate duration, has corroborating guideline studies, and is a robust study.

The acute reference dose (aRfD) and chronic reference dose (cRfD) of 0.01 mg/kg/day has been calculated from an acute neurotoxicity study in rats (Wolansky et al. 2006). The NOAEL was 1 mg/kg based on decreased motor activity. An acute endpoint for developmental toxicity was not observed in the database, and therefore the aRfD/aPAD selected for the general population is adequate to cover females 13-49. The Wolansky et al. (2006) study has also been selected for endpoint selection for short- and intermediate-term incidental oral, inhalation and dermal exposures.

2.0 Absorption, Distribution, Metabolism, and Excretion (ADME)

(See Appendix II for greater details including literature studies)

2.1 *Absorption*

The absorption of deltamethrin from the gastrointestinal tract following a single dose by oral gavage is estimated to be between 15 and 50%. The remainder is largely excreted unchanged in the feces. Following an oral gavage dose, the amount and rate of absorption can vary greatly depending on the carrier vehicle used and the volume of the dose. Studies estimating deltamethrin absorption during dietary administration are not available to compare with gavage dosing. However, based on the similarity of LOAELs between the short-term gavage studies and longer-term dietary administration studies, absorption rates and/or toxicity appear to be similar.

2.2 *Distribution*

Literature studies

Following absorption, deltamethrin is distributed throughout the body via the circulatory system, preferentially distributing to highly lipophilic tissues, such as fat. Plasma and brain reach

maximum concentrations within 1 to 2 hours after an oral gavage dose. Fat takes slightly longer to reach maximum concentrations at 2 to 4 hours. Peak fat concentrations can exceed either plasma or brain concentrations by 300-fold. Although the time to maximum concentrations may be similar between the tissue types, the elimination half-lives for plasma and brain are 15 hours while the fat may exceed 175 hours. Based on the rapid metabolism of deltamethrin in plasma and liver tissue, as discussed below, the slow release of deltamethrin from fat is likely to be inconsequential with regard to inducing neurotoxicity. However, the time to peak neurotoxicity is correlated with time to peak plasma concentration, approximately 2 hours.

Guideline studies

The fast time to peak effect following an oral bolus dose (gavage, intraperitoneal, or intravenous administration), within 2 hours, described in the literature studies is supported by the guideline acute neurotoxicity study in rats (gavage administration) and the 90-day dog study (capsule administration). Neurotoxicity was observed within 3 hours of dosing in the acute neurotoxicity study in rats including convulsions, tremors, salivation, and several FOB parameters. Neurotoxicity was observed in the 90-day dog study within 1 to 7 hours based on unsteady gait and chewing of extremities. Neurotoxicity was also evident in the rat prenatal developmental study; however, the time between dosing and initiation of neurotoxicity was not noted in the study. Neurotoxicity was also observed in the dietary administration studies. In the subchronic, subchronic neurotoxicity, and chronic toxicity rat studies, neurotoxicity was observed within the first 2 to 6 weeks. In the subchronic and chronic studies in rats and dogs, neurotoxicity decreased in the latter stages. Neurotoxicity was not observed in the developmental rabbit or carcinogenicity studies, most likely due to a combination of low dose levels and use of dietary administration.

Neurotoxic effects were not immediately evident in the dietary studies compared to the gavage. The difference is likely related to the method of deltamethrin administration. Gavage administration results in a bolus dose resulting in a large amount of deltamethrin over a short period of time. Dietary administration occurs over an entire feeding period, which may continue over several hours, diluting the effective dose. Since the plasma half-life of deltamethrin is 15 hours, it is possible that much of the chemical is metabolized prior to reaching the target tissue. Therefore, for equivalent dietary and bolus doses, the dietary administration will likely be less toxic than the bolus dose. The decreasing signs of neurotoxicity with increasing time are likely an adaptive effect. Hepatic enzymes largely responsible for the metabolism of deltamethrin are induced followed prolonged exposure, further increasing the metabolic capacity of the rats.

2.3 *Metabolism*

It is generally understood that the metabolism of pyrethroids is a detoxifying event; only the parent chemicals are capable of binding the target site for pyrethroid toxicity, i.e. axonal sodium channels. Metabolism is predominated by two mechanisms, hydrolysis and oxidation. Trans-isomers are hydrolyzed by carboxyesterases (CaEs) and cis-isomers are oxidized by hepatic P450 enzymes. However, trans-isomers are also subject to metabolism by hepatic enzymes as well.

Species-based pharmacokinetic differences for deltamethrin have been shown in the published literature. Deltamethrin is metabolized 3-fold faster in human hepatic microsomal incubations

than in comparable rat microsomal incubations *in vitro*. Humans and rodents have analogous CaEs; hydrolase A and hydrolase B in the rat, and hCE1 and hCE2 in the human. Cis-isomers, such as deltamethrin, are typically not susceptible to CaEs metabolism. However, hCE1 actively detoxifies deltamethrin, likely accounting for the increased metabolism in human microsomes. Since the endpoints selected for risk assessment are based on a rodent study, the increased deltamethrin clearance rate in humans relative to rats contributes to the conservativeness of the risk assessment for deltamethrin.

2.4 *Excretion*

In a guideline deltamethrin metabolism study, radiolabeled deltamethrin was administered to male and female SD rats. One test group received a single dose via oral gavage in corn oil at 5.50 and 0.55 mg/kg. A second group received the initial dose of radiolabeled deltamethrin, followed by 14 days of non-labeled deltamethrin at 0.55 mg/kg and then labeled compound again on day 15 (0.55 mg/kg). Seven days following administration, 31.2-56.3% of the radio-labeled deltamethrin was recovered in the urine and 35.7-58.5% was excreted in the feces. Overall recovery of dosed radioactivity was between 84.2 and 96.2%. The parent was found in the feces at 46% of the dose in the 5.50 mg/kg females and 17-35% of the dose was recovered in both sexes at all doses.

3.0 FQPA Considerations

3.1 *Adequacy of the Toxicity Database*

The toxicology database for deltamethrin is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity in rats and rabbits and a 2-generation reproduction study in rats are available for FQPA assessment. However, an immunotoxicity study as required under the revised CFR Part 158 toxicity data requirements is currently a data gap. Additionally, there are residual concerns for increased susceptibility in infants and children based on underdeveloped clearance mechanisms.

3.2 *Evidence of Neurotoxicity*

Neurotoxicity following deltamethrin dosing is observed in several guideline studies including 90-day rat and dog, prenatal developmental in the rabbit, reproduction and fertility in the rat, chronic rat and dog studies. Signs of neurotoxicity included convulsions, tremors, stumbling gait, and salivation among others. Literature studies reporting similar results support these findings. In addition, guideline neurotoxicity studies have been conducted.

3.2.1 Acute Neurotoxicity in rats

In the acute neurotoxicity study in rats, deltamethrin was administered as a single dose by gavage to Sprague-Dawley rats at 0, 5, 15, or 50 mg/kg. Neurotoxicity was observed within 3 hours of dosing. At 50 mg/kg, effects included convulsions, reduced ease of handling, salivation, impaired mobility, and reduced grip strength among others. At 15 mg/kg, neurotoxicity included salivation, impaired mobility, and no reaction to touch response. The NOAEL was 5 mg/kg.

3.2.2 Subchronic Neurotoxicity in rats

In the subchronic neurotoxicity study in rats, deltamethrin was administered to Sprague-Dawley rats at dietary levels of 0, 4, 14, or 54 mg/kg/day for 13 weeks. At 54 mg/kg/day, neurotoxicity included impaired mobility, uncoordinated righting reflex, and reduced limb strength. At 14 mg/kg/day, there were single incidences in males (soiled fur and impaired mobility). The study NOAEL was 4 mg/kg/day.

3.2.3 Developmental Neurotoxicity in rats

In an acceptable/guideline developmental neurotoxicity study, deltamethrin was administered in the diet to female Wistar rats at 0, 1.64, 6.78, or 16.1 mg/kg/day. No treatment-related effects on reproduction were noted. The maternal LOAEL was 16.1 mg/kg/day based on decreased body weight, body weight gain, and food consumption. The offspring LOAEL was 16.1 mg/kg/day based on decreased body weight and body weight gain during pre-weaning and post-weaning in males and females, increased incidence of vocalizations in males during handling and decreased fixed brain weight in females at terminal necropsy. There was no evidence of quantitative or qualitative susceptibility.

3.3 *Developmental Toxicity Studies*

Acceptable/guideline studies included a prenatal rat toxicity study, the NOAEL for maternal toxicity was 3.3 mg/kg/day based on decreased body weight and body weight gain and clinical signs of toxicity (convulsions, increased salivation, and body staining) at 7 mg/kg. At 11 mg/kg, 14 of 25 dams were sacrificed in extremis or found dead. Signs of toxicity included convulsions, increased sensitivity to external stimuli, and body surface staining. No signs of developmental toxicity were evident at 11 mg/kg, the highest dose tested (HDT), .

In a prenatal developmental study in rabbits, the NOAEL for maternal toxicity was 10 mg/kg/day based on decreased body weight gain between gestation day (GD) 6 and 21 at 32 mg/kg. There was no evidence of developmental toxicity at 32 mg/kg, the HDT.

Unacceptable/guideline developmental studies in CD-1 mice, Sprague-Dawley rats, and New Zealand White rabbits (MRID 00098092 (1976)) were considered in prior risk assessments for the purpose of assessing susceptibility. However, the receipt of acceptable/guideline studies have marginalized the contribution of these older studies. For a review of the unacceptable/guideline studies, see appendix II.

3.4 *Reproductive Toxicity Studies*

In the 2-generation reproduction study, qualitative evidence of increased susceptibility was noted at 22 mg/kg/day as effects on the F_1 generation which were not seen in the P generation or when the F_1 generation were pups but only when they were adults. Treatment-related effects in the parental animals were limited to lesions on head, neck or forelimbs (11/30) and alopecia (8/30) in the males and ataxia (22/25) and hyper sensitivity (3/25) in the females during gestation. In the F_1 generation, there were increased deaths in males (17/30) and females (19/30), clinical findings (i.e. impaired righting reflexes, hyperactivity, splayed limbs, vocalization, and excessive salivation), and cerebral congestion and/or blood clots at the highest dose tested. The clinical

findings, cerebral congestion, and blood clots were limited to the adults. The increased severity of effects in the F_1 generation was considered to be evidence of increased susceptibility. However, it is important to note the timing of the deaths in the F_1 rats; by day 4, 12/19 (males) and 9/19 (females) deaths were reported, and by day 8 postweaning, 15/17 (males) and 18/19 (females) deaths were recorded. HED has examined registrant submitted gestational data and milk transfer data for several pyrethroid chemicals. Pups receive significantly lower doses of pyrethroid through the milk than does the dam through the diet. Therefore, as the pups age and increase their intake of dosed food, there is a rapid increase in the exposure. The majority of deaths within 4 days of weaning reflect this rapid dietary uptake in deltamethrin. Furthermore, the effects were only seen at the highest dose tested, 21.6 mg/kg/day, 20-fold greater than the NOAEL selected for the acute and chronic dietary reference dose (1 mg/kg/day). Therefore, despite this evidence of increased qualitative susceptibility, a 10X for susceptibility is not warranted based on the results of the 2-generation rat study because the endpoint and dose selected for the risk assessment would be protective of the susceptibility.

3.5 *Pre- and/or Postnatal Toxicity*

There were no indications of either pre- or postnatal toxicity in the developmental or reproductive guideline studies. However, several literature studies indicate infants and children may be more susceptible to deltamethrin toxicity and are considered in a weight-of-evidence approach. As outlined below, young rats are quantitatively susceptible to deltamethrin toxicity at high doses. Doses greater than 4 mg/kg lead to lower NOAELs in the pre-adult rats. The enzymes accounting for the metabolism of deltamethrin either are not present in comparable quantities to adults, or they are not as active. Therefore, the pups do not have the capacity to detoxify deltamethrin as efficiently as adults and the pup clearance mechanisms are overwhelmed at high doses. Pups therefore demonstrate signs of neurotoxicity at doses that would be asymptomatic in adults. Similarly, enzyme profiles in infants and children are less developed than adults, and can be highly variable in quantity and activity, especially in infants. Therefore, until sufficient evidence is available demonstrating infants have the capacity to metabolize deltamethrin in a manner comparable to adults, quantitative susceptibility is assumed. It should be noted that species-specific pharmacokinetic differences have been observed between rats and humans. In vitro studies have demonstrated a 3-fold increase of deltamethrin metabolism in adult humans compared to adult rats. It has not been determined if the extrapolation of the 3-fold difference in deltamethrin metabolism is applicable to pups and infants but it indicates the rat may be a conservative model for toxicity. Furthermore, while enzyme populations may differ between infants, children, and adults, the enzyme activity in infants present at birth and through early childhood development may be sufficient to detoxify deltamethrin at rates comparable to adults for the low environmental exposures expected based on existing use patterns.

Brain Cholinergic Receptor Populations

Past risk assessments have used studies by Eriksson and Nordberg (1990) and Eriksson and Fredriksson (1991) in the weight-of-evidence for assessing susceptibility. These papers reviewed the effect of deltamethrin exposure in rats, beginning on post-natal day 10 (PND 10) and continuing for 3 weeks, on the nicotinic and muscarinic receptors in the brain. While the authors found changes in the receptor populations, the results of these studies are not appropriate for assessing susceptibility due to inconsistent results and inappropriate statistical techniques. See

appendix II for a more thorough review of these studies.

Age-dependent Susceptibility
Age-dependent susceptiblity has been demonstrated by several researchers. Sheets *et al.* (1994), administered single gavage doses of deltamethrin in corn oil to adult and weanling Long Evans rats. The effects on acoustic startle response (ASR) were examined. There was a comparable decrease in amplitude (50%) in 21- and 72-day rats at 4 mg/kg. In contrast, the LD50s for 11-, 21-, and 72-day male rats were 5.1, 11, and 81 mg/kg, respectively. The 11- and 21-day rats were therefore 16 and 7 times more sensitive than the 72-day rats to acute lethality. The authors also showed that the brain concentration of deltamethrin at death was the same for weanlings dosed with 12 mg/kg as it was for adults dosed with 80 mg/kg. At the effective dose (ED_{50}) of 4 mg/kg for ASR, the brain concentration of deltamethrin was about twice as high in weanling rats as it was in adults receiving this level.

Age-dependent Microsome and Carboxyesterase Activity
Anand and colleagues (2006) demonstrated the age-dependent clearance of deltamethrin by measuring enzymatic activity in vitro and plasma concentration *in vivo* across several age groups. *In vitro*, the ability of plasma carboxyesterases (CaE), hepatic CaEs, and hepatic microsomes to metabolize deltamethrin in PND 10, 21, 40 and 90 in male Sprague-Daley rats were characterized. Clearance values in the PND 90 rat tissues were 6-, 35-, and 7-times times greater in plasma CaE, hepatic CaE, and hepatic microsomes than the PND 10 rats. Plasma CaE activity in the 40-d rats was similar to that of the 90-d rats. However, clearance activity in the hepatic CaEs and hepatic microsomes was progressively higher in each age group. In vivo, rats were given single oral gavage doses of 10 mg/kg deltamethrin. Plasma area under the curve was highest in the PND 10 rats, progressively lower in each advancing age group, and closely correlated with signs of neurotoxicity including salivation and tremors. Similarly, hydrolase expression levels were still well below adult expression levels at PND 26 (de Zwart et al. 2008). It is important to note that the age-related toxicity appears to be a high-dose effect. At high doses, the clearance mechanisms in the rat pups were overwhelmed by the amount of deltamethrin. In low-dose situations, such as those more likely to occur in humans, the clearance mechanisms are not as likely to be overwhelmed.

Many of the carboxyesterases and P450s critical to deltamethrin metabolism are highly expressed and active in the liver. A limited amount of research into the evolution of expression and activity of these enzymes through multiple life stages ranging from birth to adult has been investigated. Pope et al. (2005) examined carboxyesterases activity in hepatic samples from humans ranging in age from 2 months to 36 years. There was a trend of increasing capacity with age but the differences between the groups were not significant. Sample sizes were limited to 5 individuals per group, increasing the variability and making statistical findings difficult. In humans, hepatic microsomal preparations, carboxyesterases hCE1 and hCE2 are primarily responsible for the clearance of deltamethrin (Godin et al. 2006). Yang et al. (2009) determined that adult expression and activity levels of hCE1 and hCE2 were 4 times greater than for children, and 10 times greater than fetal levels. Yang et al. (2009) also found high variability of the protein expression and activity within the age groups, particularly within the fetal group, sometimes ranging up to 100-fold. Sample sizes were greatly increased relative to Pope et al. (2005),

ranging from 35 to 40 per group, increasing the statistical power.

Regarding P450 enzymatic development, Hines et al. (2007, 2008) grouped several P450s into 3 categories; *i*) those that are high during gestation and fall during the first 2 years of infancy; *ii*) those that are fairly constant in expression through gestation and infancy; and *iii*) those that have low levels of expression during gestation but increase rapidly during the first 2 years of infancy. Of those cytochrome P450s identified in this study, 2C19, has also been shown to metabolize deltamethrin to a significant extent (Godin et al. 2006). 2C19 has significant expression levels throughout gestation and quickly increases within the first two years of infancy, reaching adult levels by the age of 10 (Koukouritaki et al. 2004). Whereas numerous p450s examined in the rat have minimal expression levels through gestation and do not approach the levels of adult expression until PND 10 days or later (de Zwart et al. 2008). Furthermore, several authors have noted that the expression levels of individual hepatic microsomes is highly variable from 1 to 6 months of age, often differing by more than a factor of 20-fold. Based on the development of the carboxyesterases (hCE1 and hCE2) and the P450s (2C19) critical to deltamethrin metabolism, the rat appears to be a conservative model with limited ability to metabolize deltamethrin in the early lifestages, while humans may have a greater ability to metabolize deltamethrin from birth through early childhood into adulthood.

3.6 *Determination of Susceptibility*

No quantitative or qualitative evidence of increased susceptibility, as compared to adults, of fetuses to *in utero* exposure to deltamethrin was observed in the developmental toxicity studies in rats or rabbits. There was an increase in qualitative susceptibility in the reproduction study in rats based on increased mortality in the F1 pups. However, the effects only occurred when the weanlings increased their intake of deltamethrin through the feed and at doses much higher than currently used for risk assessment. In contrast, several literature studies indicate age-dependent sensitivity to deltamethrin based on reduced capacity of metabolic enzymes in juveniles.

3.7 *Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility*

The purpose of the Degree of Concern analysis is: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by an FQPA safety factor and, if so, the size of the factor needed.

The capacity of rats to metabolize deltamethrin appears to be minimal at birth, increasing to near adult levels by 10 or 20 days of age. Conversely, human infants appear to be afforded more protection by higher expression levels of enzymes at birth and through infancy. However, human infants, similar to rats, do not reach full expression levels of the carboxyesterases and microsomes for approximately 10 years. Furthermore, the levels of expression of the protective cytochromes appear to be highly variable during the first 6 months of infancy. Therefore, retention of the FQPA factor is appropriate based on *i*) increased sensitivity in humans due to

decreased capacity for deltamethrin metabolism until 10 years of age; and *ii*) highly variable expression levels of microsomes in humans from 1 to 6 months of age

4.0 FQPA Safety Factor for Infants and Children

HED recommends the 10X FQPA SF be retained after evaluating the toxicological and exposure data for deltamethrin. This recommendation is based on the following:

- The toxicological data base is adequate for FQPA assessment. However, an immunotoxicity study is now required as part of the new part 158 guidelines.

- There are residual uncertainties for post-natal toxicity with respect to infants and children. Literature studies indicate the enzymes responsible for the detoxification of deltamethrin are at lower levels of activity in children than are present in adults.

- The dietary food exposure assessment is based on assumptions designed to produce results that will not underestimate dietary exposure.

- The dietary drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

No signs of immunotoxicity were observed in the submitted studies, so there is no need to retain an additional uncertainty factor for the lack of the required study. In addition, the 10X FQPA factor has been retained for susceptibility of infants and children, and would account for any uncertainty with respect to potential immunotoxicity.

5.0 Hazard Identification and Toxicity Endpoint Selection

5.1 *Endpoint Selection and Uncertainty Factors for Risk Assessment*

One study was used for endpoint selection for acute and chronic dietary, incidental oral, and short- and intermediate-term dermal and inhalation exposure and risk assessment. Based on the age-dependent susceptibility described in section 3.0, a 10X FQPA safety factor has been retained for infants and children in all appropriate exposure scenarios.

Study: Acute Neurotoxicity in Rats – Motor Activity; Wolansky et al. (2006)

Study Summary: Acute oral dose-response functions were determined in adult male Long Evans rats for eleven pyrethroids, including deltamethrin (n = 8–18 per dose; deltamethrin dose levels 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg, vehicle = corn oil, at 1 ml/kg). Motor function was measured using figure-8 mazes. For deltamethrin, testing began two hours following dosing and lasted for one hour. The dose which caused a 30% decrease in motor activity (ED30) for deltamethrin was 2.51 mg/kg. The NOAEL, 1 mg/kg, is an estimate of the highest no-effect dose level at which treated rats did not display any decrease in motor activity. The ED30 and NOAEL

are estimates generated from a dose-response curve, similar to a benchmark dose (BMD) analysis.

Dose and Endpoint for Establishing a RfD: 1.0 mg/kg (NOAEL) based on reduced motor activity in male rats.

Uncertainty Factors:

aRfD, cRfD, Residential Dermal and Inhalation:

General Population – 100X (10X interspecies extrapolation, 10X intraspecies variability)
Infants and Children up to 13 years – 1000X (10X interspecies extrapolation, 10X intraspecies variability, 10X FQPA)

Incidental Oral:

Infants and Toddlers - 1000X (10X interspecies extrapolation, 10X intraspecies variability, 10X FQPA)

Occupational Dermal and Inhalation:

General Population – 100X (10X interspecies extrapolation, 10X intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factor:

Justification of Motor Activity Endpoint for Multiple Exposure Scenarios

Endpoints for risk assessment are not typically selected from literature studies. However, the Wolansky et al. (2006) study is uniquely appropriate based on: 1) the large number of dose levels (6); the large number of animals (8-18 per group); 3) neurotoxicity was determined at the time to peak effect (2 hours post dosing); and 4) motor activity is recognized as one of the most common techniques for determining pyrethroid neurotoxicity in laboratory animal studies (Wolansky and Harrill 2008). Furthermore, the selection of 1 mg/kg NOAEL from an acute oral study is supported by multiple guideline and literature studies.

i) Low potential for bioaccumulation. As discussed in section 3.2, deltamethrin has a rapid clearance value and short half-life *in vivo* with minimal chance to bioaccumulate. Subchronic and chronic repeated doses are therefore essentially a series of acute doses. Similar LOAELs were observed for the acute, subchronic, and chronic studies.

ii) Supporting Guideline Studies. Three guideline studies share the NOAEL of 1 mg/kg/day based on neurotoxicity and decreased body weight/body weight gain; the subchronic rat, subchronic dog, and the chronic dog. Dose levels in the subchronic rat included 0, 0.1, 1.0, 2.5, and 10.0 mg/kg/day. The LOAEL of 2.5 mg/kg/day was based on decreased body weight gains in males and signs of neurotoxicity (hypersensitivity to noise by week 3 and decreasing throughout the remaining 10 weeks). Dose levels in the subchronic dog included 0, 0.1, 1.0, 2.5, and 10.0 mg/kg/day. The LOAEL of 2.5 mg/kg/d was based on decreased body weight gain and signs of neurotoxicity (salivation, unsteadiness, tremors, and jerking movements by 1 to 7 hours postdosing). Neurological effects became less prominent during study progression. Dose levels in the chronic dog study included 0, 1, 10, and 50 mg/kg/day. The LOAEL of 10 mg/kg/day was based on reduced body weight gain and clinical signs (chewing of extremities, and liquid feces).

Neurological effects were found during the first 13 weeks of the study but decreased to sporadic events by weeks 26 and 52.

iii) Supporting Literature Studies
Following acute oral gavage of deltamethrin, motor activity was reduced at 3 mg/kg. The study NOAEL was 1 mg/kg (Crofton et al. 1995). In a high-dose acute oral study determined to differentiate signs of neurotoxicity between Type I and Type II pyrethroids, BMD analysis determined a lower limit of deltamethrin toxicity in rats of 15.4±11.5 mg/kg (US EPA, 2007). Dose spacing did not allow the determination of a NOAEL; however, the BMDL is similar to LOAELs observed in other rat studies.

Justification for Dermal Assessment
Residential and occupational short- and intermediate-term dermal exposure is anticipated for deltamethrin. Typically, dermal assessments are not required when a route-specific dermal study indicates no systemic toxicity at the limit dose and there are no developmental concerns, as is the case for deltamethrin. However, the 21-day dermal study in rats was not considered for endpoint selection because the critical toxic effect, neurotoxicity, was not evaluated, and therefore use of the study would not be protective of potential neurotoxicity via the dermal route.

ii) Determination of the oral equivalent dose for the 21-day dermal study in rats. A dermal absorption rate of 1% is based on the ratio of an oral study LOAEL and the dermal study NOAEL. The subchronic toxicity study in rats was chosen because it is of similar duration to the dermal study; it used the same species (rat); and the effect observed was neurotoxicity. If a LOAEL had been available for the dermal toxicity test, it would have likely been based on neurotoxicity similar to many of the guideline studies.

Estimated Dermal Absorption Rate;

$$= \frac{10\ mg/kg/day\ (LOAEL\ subchronic\ toxicity\ study\ in\ rats)}{1000\ mg/kg/day\ (NOAEL\ 21\text{-}day\ dermal\ study\ in\ rats)}$$

$$= 0.01 \text{ or } 1\ \%$$

The oral equivalent dose is calculated from the dermal exposure NOAEL (1000 mg/kg) and the estimated absorption factor of 1%;

Oral Equivalent Dose for Dermal Study = (1000 mg/kg/day) X (0.01 Absorption)

= 10 mg/kg/day

HED concluded the 21-day dermal study with a NOAEL of 1000 mg/kg/day is not protective of neurotoxicity observed in the equivalent oral studies because the equivalent oral dose (10 mg/kg) is greater than the point of departure selected for risk assessment (1 mg/kg) and therefore would

not be protective.

ii) Potential Susceptibility in Infants and Children. The 21-day dermal toxicity study in rats was conducted using adult rats. However, HED has concluded infants and children have increased susceptibility to deltamethrin relative to adults. Therefore, the NOAEL determined in adults may not be appropriate for pups. Due to the immature clearance mechanisms in pups, a 1000 mg/kg/day dermal exposure in pups may produce toxicity absent in adults at an equivalent dose.

Inhalation
An appropriate inhalation toxicity study was not available for endpoint consideration. A default inhalation absorption factor of 100% was used for risk assessment.

5.2 *Level of Concern for Margin of Exposure*

Table 3.5.8 Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Residential and Occupational Exposure			
Incidental Oral	1000	1000	N/A
Dermal-Adults	100	100	N/A
Inhalation-Adults	100	100	N/A
Dermal-Infants & Children	1000	1000	N/A
Inhalation- Infants & Children	1000	1000	N/A

5.3 *Recommendation for Aggregate Exposure Risk Assessments*

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessments must consider exposure from three major sources: oral, dermal and inhalation. All routes of exposure for all durations of exposure can be aggregated based on the common endpoint observed throughout the database (decreased motor activity).

5.4 *Classification of Carcinogenic Potential*

There was no evidence of carcinogenicity in cancer studies with mice and rats. Therefore, in accordance with EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), deltamethrin is classified as "not likely to be carcinogenic to humans."

5.5 *Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Human Risk Assessments*

Table A.1.a. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, excluding Infants and Children)	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Acute RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	The endpoint, decreased motor activity in male rats, is taken from an acute oral study (Wolansky et al. 2006). Using a nonlinear exponential threshold additivity model, a NOAEL (aka threshold dose) was obtained by fitting motor activity data across 7 dose groups; 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg. The NOAEL is an estimate of the highest no-effect dose level at which treated rats would not display any decrease in motor activity. Supported by subchronic rat, subchronic dog and chronic dog studies with NOAELs of 1 mg/kg/day and LOAELs of 2.5 or 10 mg/kg/day based on signs of neurotoxicity including unsteadiness, tremors and jerking movements, salivation, and chewing on extremities (chronic dog only).
Acute Dietary (Infants and Children)	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=10x	Acute RfD = 0.01 mg/kg/day aPAD = 0.001 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	No appropriate endpoint available
Chronic Dietary (All populations, excluding infants and children)	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x	Chronic RfD = 0.01 mg/kg/day cPAD = 0.01 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Chronic Dietary (Infants and children)	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=10x	Chronic RfD = 0.01 mg/kg/day cPAD = 0.001 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.

Table A.1.a. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral; Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=10x	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Dermal (General population excluding infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x DAF: 1%	Residential LOC for MOE = 100	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Dermal (Infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=10x DAF: 1%	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Inhalation (General population excluding infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=1x IAF: 100%	Residential LOC for MOE = 100	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Inhalation (Infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF=10x IAF: 100%	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al. 2006). See Acute Dietary-General population for supporting information.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. DAF = Dermal absorption factor. IAF = Inhalation absorption factor. N/A = not applicable.

Table A.1.b. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x DAF: 1%	Occupational LOC for MOE = 100	Acute Motor Activity Study in Rats (Wolansky et al., 2006), based on decreased motor activity in adult male rats. Using a nonlinear exponential threshold additivity model, a NOAEL (aka threshold dose) was obtained by fitting motor activity data across 7 dose groups; 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg. The NOAEL is an estimate of the highest no-effect dose level at which treated rats would not display any decrease in motor activity. Supported by subchronic rat, subchronic dog and chronic dog studies with NOAELs of 1mg/kg/day and LOAELs of 2.5 or 10 mg/kg/day based on signs of neurotoxicity including unsteadiness, tremors and jerking movements, salivation, and chewing on extremities (chronic dog only).
Inhalation All Durations	NOAEL= 1 mg/kg/day	UF_A= 10 x UF_H=10 x IAF: 100%	Occupational LOC for MOE = 100	Acute Motor Activity Study in Rats (Wolansky et al., 2006), based on decreased motor activity in adult male rats. See Dermal for supporting information.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. DAF = Dermal absorption factor. IAF = Inhalation absorption factor. N/A = not applicable.

6.0 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee

(EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, deltametnrin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Appendix I. Profile Tables for Deltamethrin Toxicity Studies

Profile of Acute Deltamethrin Toxicity Studies

Table 3. Acute Toxicity of Deltamethrin

Guideline Number	Study	MRID	Results	Acute Tox Category
870.1100	Acute Oral Rat	41651019	LD_{50} = >5000 mg/kg in 1% aqueous methyl cellulose	IV
		00070734	LD_{50} = 66.7 mg/kg (males) = 86 mg/kg (females) in polyethylene glycol LD_{50} = 128.5 mg/kg (males) = 138.7 mg/kg (females) in sesame oil	II
870.1200	Acute Dermal Rat	41651020	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation Rat	41651021	LC_{50} = 2.2 mg/L	III
		00070734	LC_{50} = 0.6 mg/L	II
870.2400	Primary Eye Irritation Rabbit	41651022	mild/mod irritant	III
870.2500	Primary Skin Irritation Rabbit	41651023	not a dermal irritant	IV
870.2600	Dermal Sensitization Guinea Pig	41651024	not a dermal sensitizer	NA

Profile of Deltamethrin Toxicity Studies

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
870.3100 90-Day oral toxicity-rat	00098103 (1977) M&F: 0, 0.1, 1.0, 2.5, 10.0 mg/kg/day Acceptable/nonguideline (stability and purity data absent, dose levels did not produce sufficient toxicity)	NOAEL = M: 1/10 (M/F) mg/kg/day LOAEL = M: 2.5 mg/kg/day based on decreased body weight gains in males; neurological toxicity (righting reflex, placing and gripping reflexes, locomotion and motor strength, behavior changes and response to noise (hypersensitivity)) in 2.5 and 10 mkd groups; effects decreased over 13-week study
870.3150 90-Day oral toxicity-dog	00098104 (1977) **Unacceptable/nonguideline** (agent purity not listed, too few animals (n=4 per group), number of required observations were absent) M&F: 0, 0.1, 1.0, 2.5, 10 mg/kg/day	NOAEL = M&F: 1 mg/kg/day LOAEL = M&F: 2.5 mg/kg/day based on CNS effects, diarrhea, vomiting and decreased body weight gain; CNS effects including salivation, unsteadiness, tremors and jerking movements observed 1 to 7 hours after dosing in 2.5 and 10 mg/kg dose groups. [Effects declined over 13-week testing period.]
870.3200 21-Day dermal toxicity-rat	42773901 Acceptable/guideline M&F: 0, 100, 300, 1000 mg/kg/day	**Systemic** NOAEL = M &F: > 1000 mg/kg/day (limit dose) The **dermal** NOAEL was not established: signs of local irritation seen at all doses. The **dermal** LOAEL = 100 mg/kg/day
870.3250 90-Day dermal toxicity	NA	NA

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
21-Day inhalation toxicity-rat	00098089 **Unacceptable/non-guideline** M&F: 0, 3, 9.6, 56.3 µg/l for 6 h/day for 5 days/week	NOAEL = M&F: 3 µg/L LOAEL = M&F: 9.6 µg/L based on decreased body weight gain, nervous system stimulation and skin irritation
870.3700a Prenatal developmental-rat	41651025 (1990) Acceptable/guideline F: 1.0, 3.3, 7, 11 mg/kg/day	**Maternal** NOAEL = 3.3 mg/kg/day LOAEL = 7 mg/kg/day based on decreased body weight and body weight gain and clinical signs of toxicity 9 convulsions, increased salivation, body staining; At 11 mkd, 14/25 dams sacrificed in extremis or found dead, convulsions, increased sensitivity to external stimuli, body surface staining. **Developmental** NOAEL >11 mg/kg/day LOAEL was not observed
	00098092 (1976) **Unacceptable/guideline** (not noted if increases in delayed ossification were noted in fetal and/or litter incidences; neither route of administration or vehicle noted) F: 0, 0.1, 1.0, 10 mg/kg/day	**Maternal** NOAEL = 1.0 mg/kg/day LOAEL = 10 mg/kg/day based on slightly reduced body weight. **Developmental** NOAEL = 1.0 mg/kg/day LOAEL = 10 mg/kg/day based on delayed ossification of the sternebrae; fetal losses increased from controls (2.2, 2.6, 2.7, and 4%), though not statistically different.

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
870.3700b Prenatal developmental-mouse	00098092 (1976) **Unacceptable/guideline** (not noted if increased in delayed ossification were noted in fetal and/or litter incidences) F: 0, 0.1, 1.0, 10 mg/kg/day	**Maternal** NOAEL = ≥10 mg/kg/day LOAEL was not observed. **Developmental** NOAEL = 0.1 mg/kg/day LOAEL = 1.0 mg/kg/day based on decreased fetal weight, and delayed ossification of the sternebrae and paws
870.3700b Prenatal developmental-rabbit	41651026 (1990) **Unacceptable**/guideline F: 0, 10, 25, 100 mg/kg/day in carboxymethylcellulose	**Maternal** NOAEL = 100 mg/kg/day LOAEL = was not established. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on increases in delayed ossification and skeletal variations
	00098092 (1976) **Unacceptable**/guideline (neither route of administration or vehicle noted; details of teratogenic parameters examined not given) F: 0, 1, 4, 16 mg/kg/day	**Maternal** NOAEL = ≥16 mg/kg/day LOAEL was not observed **Developmental** NOAEL = 4 mg/kg/day LOAEL = 16 mg/kg/day based on decreased fetal weights and increased fetal loss (6.6, 18.5, 15.5, 10.2, 27.4%)
870.3700b Prenatal developmental-rabbit	45881901 (2001) Acceptable/guideline F: 0, 3, 10, 32 mg/kg/day in corn oil	**Maternal** NOAEL = 10 mg/kg/day **Maternal** LOAEL = 32 mg/kg/day based on decreased body weight gain between GD 6 and 21. **Developmental** NOAEL ≥ 32 mg/kg/day **Developmental** LOAEL = not established

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
870.3800 Reproduction and fertility effects-rats	44398101 (1992) Acceptable/guideline M&F: 0, 5, 20, 80, 320 ppm Parental animals M: 0, 0.3, 1.3, 5.4, 21.2 mg/kg/day F: 0, 0.4, 1.5, 6.1, 23.5 mg/kg/day F_1 animals M: 0, 0.4, 1.4, 5.8, 24.9 mg/kg/day F: 0, 0.4, 1.7, 6.7, 27.2 mg/kg/day	**Parental/Systemic** NOAEL = M: 5.4; F: 6.1 mg/kg/day **Parental/Systemic** LOAEL = M: 21.2; F: 23.5 mg/kg/day based on increased mortality and clinical signs (ataxia, hyperactivity, vocalizations, excessive salivation), decreased body weights, body weight gains, and absolute food consumption, and gross pathological findings in F1 males and females (cerebral congestions and/or blood clots (9-12/28)) **Offspring** NOAEL = M: 5.8; F: 6.7 mg/kg/day **Offspring** LOAEL = M: 24.9; F: 27.2 mg/kg/day based on increased pup mortality and decreased body weights and body weight gains **Reproductive** NOAEL = M: ≥24.9; F: 27.2 mg/kg/day **Reproductive** LOAEL = M: ≥21.2; F: 23.5 mg/kg/day
870.4100a Chronic toxicity-rat	Same as Chronic Toxicity/Carcinogenicity- rat see below (870.4300)	See below (870.4300)

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
870.4100b Chronic toxicity-dog	44372601 (1993) Acceptable/guideline M&F: 0, 1, 10, 50 mg/kg/day (gelatin capsule) -52 weeks	NOAEL = M&F:1 mg/kg/day LOAEL = M&F:10 mg/kg/day based on reduced body weight gain, chewing and scratching of extremities, and liquid feces; treatment-related decreases in body weight gain throughout the study in males and females in the 10 and 50 mg/kg/d dose groups; early clinical signs in 10 and 50 mg/kg/d groups including chewing at extremities, abnormal gait (50 mkd) and liquid feces; and neurological effects in 50 mg/kg/d group at weeks 26 and 52.
870.4200b Carcinogenicity-mouse	44372602 (1995) Acceptable/guideline M&F: 0, 10, 100, 1000, 2000 ppm M: 0, 1.5, 15.7, 155.4, 314.8 mg/kg/day F: 0, 2.0, 19.6, 189.3, 395.1 mg/kg/day	NOAEL = M&F: 2000 ppm (HDT) LOAEL was not established **No evidence of carcinogenicity, HDT assumed to be adequate to characterize the carcinogenic potential based on a 12-week toxicity study in mice showing death and body weight differences (13% decrease) at 3000 ppm**
870.4300 Chronic/ Carcinogenicity-rat	44398102 (1995) Acceptable/guideline M&F: 0, 25, 125, 500, 800 ppm M: 0, 1.1 5.4, 22.2, 35.9 mg/kg/day F: 0, 1.5, 7.3, 29.5, 47.1 mg/kg/day	NOAEL = M&F: 800 ppm (HDT) LOAEL was not established **No evidence of carcinogenicity, HDT assumed to be adequate to characterize the carcinogenic potential based on a 13-week toxicity study in rats showing death, reduced body weight gains and marked neurological disturbances at ≥1000 ppm**

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
	00098105 (1980) **Unacceptable**/guideline M&F: 0, 2, 20, 50 ppm M&F: 0, 0.1, 1.0, 2.5 mg/kg/day	NOAEL = M&F: >50 ppm (HDT) LOAEL was not determined **No evidence of carcinogenicity**
870.5100 Bacterial reverse mutation test- *S. typhimurium*	42475902 (1980) Acceptable/guideline 0, 2, 10, 50, 200, 1000, 5000 µg/plate +/- S9	There was no evidence of an induced mutagenic effect at concentrations up to the limit dose (5000 µg/plate +/-S9). Compound precipitation seen at ≥200 µg/plate.
870.5375 In vitro mammalian chromosome aberration test- Chinese hamster ovary (CHO) cells	41651027 (1989) Acceptable/guideline 0, 19, 38, 75, 150 µg/mL +/- S9	There was no evidence of an induced mutagenic effect up to cytotoxic concentrations (≥38 µg/mL -S9; 150 µg/mL +S9). Levels ≥75 µg/mL were insoluble.
Other Genotoxicity 870.5550 Bacterial DNA damage/repair- *E. coli*	42475902 Acceptable/guideline 0, 1250, 2500, 5000 µg/well +/- S9	There was no evidence of DNA repair/damage up to the limit dose (5000 µg/well +/-S9). Compound precipitation seen at ≥200 µg/well.
Other Genotoxicity 870.5550 UDS in primary rat hepatocytes	41651028 (1989) Acceptable/guideline 0, 0.13, 4.2, 13, 42, 130, 420, 1300, 4200 µg/mL	There was no evidence that unscheduled DNA synthesis was induced up to insoluble concentrations (≥130 µg/mL).
870.6200a Acute neurotoxicity screening battery-rats	44557901 (1998) Acceptable/guideline M&F: 0, 5, 15, 50 mg/kg	Neurotoxic NOAEL= 5 mg/kg/day LOAEL = 15 mg/kg/day based on salivation, soiled fur, impaired motility, no reaction to approach or touch response in FOB
870.6200b Subchronic neurotoxicity screening battery	44557902 (1998) Acceptable/guideline M&F: 0, 50, 200, 800 ppm M: 0, 4, 14, 54 mg/kg/day F: 0, 4, 16, 58 mg/kg/day	Neurotoxic NOAEL= M: 14; F: 16 mg/kg/day LOAEL = M: 54; F: 58 mg/kg/day based on mortality, clinical signs, FOB findings, and decreased body weights, body weight gains, and food consumption

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
870.6300 Developmental neurotoxicity	46814301 (2006) Acceptable/Non-Guideline (pending review of positive-control data) 0, 20, 80, 200 ppm 0, 1.6, 6.8, 16.1 mkd (gestation and lactation)	**Maternal NOAEL** = 80 ppm (6.8 mkd) **Maternal LOAEL** = 200 ppm (16.1 mkd) based on decreased body weight gain and food consumption **Offspring NOAEL** = 80 ppm (6.8 mkd) **Offspring LOAEL** = 200 ppm (16.1 mkd) based on decreased body weight and body weight gain during pre-weaning and post-weaning in males and females, increased incidence of vocalizations (males) during FOB handling and decreased fixed brain weight in females at the terminal necropsy.
870.7485 Metabolism and pharmacokinetics-rats	41651001 (1990) Acceptable/guideline M&F: 0.55, 5.5 mg/kg	The test material was relatively well absorbed. Excretion was almost complete within 48 hours. Approximately 36-59% of the dose was found in feces and an approximately equal amount in urine. Absorbed deltamethrin was cleaved by hydrolysis at the ester site followed by rapid sulfate and glucuronide conjugation.
870.7600 Dermal penetration	NA	NA
Literature studies		

Table 4. Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/Classification /Doses**	**Results**
Wolansky et al. (2006)	0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg Vehicle: Corn oil Volume: 1 ml/kg	Threshold dose of 1 mg/kg based on Acute Motor Activity Study in Rats (Wolansky et al., 2006), based on decreased motor activity in adult male rats. Using a nonlinear exponential threshold additivity model, a NOAEL (aka threshold dose) was obtained by fitting motor activity data across 7 dose groups; the NOAEL is an estimate of the highest no-effect dose level at which treated rats would not display any decrease in motor activity.

Abbreviations Used:
NOAEL = No Observed Adverse Effect Level
LOAEL = Lowest Observed Adverse Effect Level
HDT = Highest Dose Tested
MTD = Maximum Tolerated Dose
FOB = Functional Observation Battery

Appendix II: Literature Studies

Detailed Study Reviews: Absorption, Distribution, Metabolism, and Excretion

Absorption

The ADME of pyrethroids is generally characterized in the literature. Bioavailability following oral gavage dosing has been estimated at 14 and 18% by Anadon et al. (1996) and Kim et al. (2008), respectively. Estimates for other pyrethroids, including permethrin at 61% (Anadón et al. 1991) and λ-cyhalothrin at 67% (Anadón et al. 2006), are far greater. In a guideline rat metabolism study, ≥ 31.2% of the deltamethrin was absorbed following a single oral gavage in corn oil based on urinary excretion.

The route and nature of deltamethrin administration can greatly influence the absorption and pharmacokinetics. Several studies have demonstrated the effect vehicle and volume can have on acute dosing. Crofton et al. (1995) compared the potency of deltamethrin following oral and intraperitoneal (IP) in one of four vehicles (corn oil, glycerol formal, Emulphor, or methylcellulose). Corn oil and glycerol formal resulted in the lowest effective dose (3.0 mg/kg oral; 30 and 1 mg/kg IP) and methylcellulose rendered deltamethrin nearly non-toxic (>1000 mg/kg oral; 100 mg/kg IP). IP administration resulted in a quicker time to peak effect for all vehicles. Similarly, Kim et al. (2007) demonstrated the oral and iv bioavailability of deltamethrin was 9-fold greater when administered in glycerol formal vehicle compared to the more aqueous Alkamuls vehicle. Comparable doses in glycerol formal resulted in moderate toxicity while rats receiving deltamethrin in Alkamus were asymptomatic. Kim et al. (2008) and colleagues compared the distribution of deltamethrin in rats following a single oral dose and an IV at 2mg/kg in glycerol formal. IV administration resulted in 6-fold greater total plasma concentration. Finally Wolansky et al. (Wolansky et al. 2007) demonstrated a 2-fold increase in bifenthrin (Type I pyrethroid) potency when administered via oral gavage at 1 ml/kg relative to 5 ml/kg.

While it is difficult to directly compare the gavage exposures described above with dietary administrations due to the differences in duration (gavage is a bolus dose whereas dietary administration may take 12 hours to ingest a similar dose based on feeding habits), it can also be inferred that dietary administration can alter the absorption, pharmacokinetics, and toxicity of deltamethrin. However, this has not been demonstrated by the guideline studies performed with deltamethrin since the gavage and dietary administration studies had similar NOAELs.

Distribution

Following absorption, pyrethroids preferentially distribute to highly lipophilic tissues, such as fat. Following acute oral gavage doses of 0.4, 2, or 10 mg/kg deltamethrin, maximum concentrations in the brain, plasma, and fat were dose-dependent. Deltamethrin concentrations in the brain were less than in plasma, and concentrations in the fat were several times greater than in plasma. Elimination half-lives were similar for the 2 and 10 mg/kg dose groups; approximately 15 hours for brain and plasma and 175 hours for adipose tissue (Kim et al. 2008). In contrast, following a single oral gavage of 26 mg/kg, brain tissue accumulated deltamethrin to much greater extent than plasma, up to 300-fold (Anadón et al. 1991). Half-lives were considerably slower in the

Anadon et al.(1991) study at 38.5 hours for plasma and 24-41 hours for regional sections of the brain. Regardless, the time to peak tissue concentrations were similar between the studies. Brain and blood deltamethrin concentrations peaked between 1 and 2 hours after dosing (Anadón et al. 1996; Kim et al. 2008) and adipose tissue peaked between 2 and 6 hours after dosing (Kim et al. 2008). The time to peak concentrations in the plasma and blood corresponds with time to peak effect for neurotoxicity following acute oral gavage recorded in literature studies (Anand et al. 2006; Wolansky et al. 2006).

The fast time to peak effect following an oral bolus dose (gavage, intraperitoneal, or intravenous administration), within 2 hours, described in the literature studies is supported by the guideline acute neurotoxicity study in rats (gavage administration) and the 90-day dog study (capsule administration). Neurotoxicity was observed within 3 hours of dosing in the acute neurotoxicity in rats based on tremors, convulsions, salivation, impaired mobility and a lack of reaction to touch response in the FOB. Neurotoxicity was observed in the 90-day dog study within 1 to 7 hours based on unsteady gait and chewing of extremities. Neurotoxicity was also evident in the rat prenatal developmental study; however, the time between dosing and initiation of neurotoxicity was not noted in the study. As previously noted, it is difficult to compare dietary administration with bolus administration due to the difference in ingestion rates; bolus = immediate; dietary = possibly over a 12 hour span. The issue is further complicated by the effect diet may have on deltamethrin absorption rate from the gastrointestinal tract. However, neurotoxicity was observed in the dietary administration studies as well. In the subchronic toxicity in rats, subchronic neurotoxicity, and chronic toxicity rat studies, neurotoxicity was observed within the first 2 to 6 weeks; unlike the short term (< 22 days) studies previously described, neurotoxicity decreased in the later stages. Neurotoxicity was not observed in the developmental rabbit or carcinogenicity studies, most likely due to a combination of low dose levels and dietary administration.

Neurotoxic effects were not immediately evident in the dietary studies compared to the gavage. The difference is likely related to the method of deltamethrin administration. Gavage administration results in a bolus dose resulting in a large amount of deltamethrin over a short period of time. Dietary administration occurs over an entire feeding period, which may continue over several hours. Therefore, the deltamethrin is being metabolized before reaching target tissue to a much greater extent than occurs in gavage studies. Maximal target tissue concentrations will be much lower in dietary feeding studies than gavage administration of comparable doses, decreasing neurotoxicity. The decreasing signs of neurotoxicity with increasing time are likely an adaptive effect. Hepatic enzymes largely responsible for the metabolism of deltamethrin are induced followed prolonged exposure, further increasing the metabolic capacity of the rats.

Metabolism

Deltamethrin metabolism is a detoxifying event. The metabolites have not been shown to be neurotoxic. Only the parent chemical is capable of binding the target site (axonal sodium channels). Metabolism is predominated by two mechanisms, hydrolysis of the ester bond and oxidation. Trans-isomers are predominantly metabolized by hydrolysis; hydrolases A and B in the rat and hCE1 and hCE2 in the human (Ross et al. 2006). Cis-isomers are predominantly

metabolized by oxidation of hepatic P450 enzymes, specifically 1A1, 1A2, 2C6, 2C11, 3A2 in the rat (Anand et al. 2006; Godin et al. 2007) and 2C8, 2C19, and 3A5 in humans (Godin et al. 2007). These lists are not conclusive as trans-isomers are subject to metabolism by hepatic enzymes and additional enzymes contribute to overall pyrethroid metabolism.

Species-based pharmacokinetic differences for deltamethrin have been shown. *In vitro*, Godin and colleagues (2006) incubated deltamethrin in human and rat hepatic microsomal preparations. The human incubate metabolized deltamethrin 3-fold faster than did the rat microsomal incubations. Typically, the cis-isomers pyrethroids, such as deltamethrin, are metabolized primarily via oxidative mechanisms (e.g. cytochrome P450s). However, in the Godin et al. (2006) study, deltamethrin was predominantly metabolized by the carboxyesterase component of the hepatic incubations. Ross et al. (2006) determined that hCE1 has a high affinity for deltamethrin, much higher than either hCE2 (human) or hydrolase A or hydrolase B (rat) carboxyesterases, accounting for the enhanced clearance in human hepatic tissue. Since the endpoints selected for risk assessment are based on a rodent study, the increased deltamethrin clearance rate in humans relative to rats contributes to the conservativism in the risk assessment for deltamethrin.

Excretion
In a guideline deltamethrin metabolism study, radiolabeled deltamethrin was administered to male and female SD rats. One test group received a single dose via oral gavage in corn oil at 5.50 and 0.55 mg/kg. A second group received the initial dose of radiolabeled deltamethrin, followed by 14 days of non-labeled deltamethrin at 0.55 mg/kg and then labeled compound again on day 15 (0.55 mg/kg). Seven days following administration, 31.2-56.3% was recovered in the urine and 35.7-58.5% was excreted in the feces. Overall recovery of dosed radioactivity was between 84.2-96.2%. The parent was found in the feces at 46% of the dose in the 5.50 mg/kg females and 17-35% of the dose was recovered in both sexes at all doses.

Evidence of Pre- or Post-Natal Susceptibility

Unacceptable/guideline Developmental Studies in Mice, Rats, and Rabbits
These studies were considered in the weight-of-evidence argument for maintaining a safety factor based on increased susceptibility pups in previous deltamethrin risk assessments. However, they were not used for endpoint selection in the current risk assessment because more recent acceptable/guideline studies have been submitted, and because the studies were considered deficient in one way or another, thereby marginalizing their contribution to the overall hazard characterization.

The results of developmental studies in CD-1 mice, Sprague-Dawley rats, and New Zealand White rabbits were reported in MRID 00098092 (1976). These studies were considered to be "unacceptable/guideline." Neither the route of administration nor vehicle used for mice was specified, nor the route(s) of administration for rats and rabbits indicated. Mice were dosed at 0, 0.1, 1.0 or 10 mg/kg/day; maternal LOAEL not observed, NOAEL ≥ 10 mg/kg/day. The developmental LOAEL was 1.0 mg/kg/day based on an increased incidence (fetal and/or litter) of delayed ossification of the sternebrae and paws together with decreased fetal body weights, the

NOAEL = 0.1 mg/kg/day. In the rat study (0, 0.1, 1.0 or 10 mg/kg/day), maternal LOAEL was 10 mg/kg/day based on slightly reduced body weights; the NOAEL was 1.0 mg/kg/day. The developmental LOAEL was equivocally set at 10 mg/kg/day based only on a statistically significant increase in incidence (fetal and/or litter) of delayed ossification of the sternebrae, the NOAEL = 1.0 mg/kg/day. The rabbits were dosed at 0, 1, 4 or 16 mg/kg/day. The maternal LOAEL was not observed, the NOAEL was ≥ 16 mg/kg/day. The developmental LOAEL was 16 mg/kg/day based on increased fetal losses and decreased fetal weights, the NOAEL was 4 mg/kg/day.

Regarding these three studies, while they were unacceptable and did not provide a robust assessment of fetal sensitivity, the developmental effects seen in mice (i.e., delayed ossification and decreased fetal body weights), rats (i.e., delayed ossification) and rabbits (i.e., increased fetal loss or decreased fetal body weight) appeared to occur either in the absence of maternal toxicity (mice or rabbits) or the presence of mild maternal toxicity (slightly reduced maternal body weight in rats). These studies were used in the weight-of-the-evidence analysis of increased susceptibility in prior risk assessments.

The methods of administration have been shown to influence the extent of toxicity. Crofton *et al.* (1995) orally or intraperitoneally (IP) administered deltamethrin (>97%) prepared in corn oil, Emulphor, glycerol formal, or methylcellulose to Long Evans male rats. The different vehicles were tested because of the lipophilic properties of deltamethrin, and the evidence that different vehicles change the amount of toxicity observed. Animals were exposed to motor activity testing (figure-8 maze with photodetectors-1 hour period) at various times after dosing. There were dose-related reductions in motor activity regardless of the vehicle, and the IP route was more effective than the oral route for all vehicles except corn oil. The peak effect was attained between 1 and 2 hours post administration. Corn oil was the most effective oral vehicle, with methylcellulose being the least effective. Kim et al. (2007) had similar findings when comparing two vehicles following oral gavage; glycerol formal and Alkamuls. The bioavailability of deltamethrin in the aqueous Alkamuls solution was 9-fold lower than in the glycerol formal.

Therefore, without knowledge of administration route and vehicle, these studies are precluded from for endpoint selection. The potential for route of administration to impact sensitivity to developing young has not been investigated for pyrethroids. However, the susceptibility noted in the mouse and rabbit studies is in contrast to more recent acceptable/guideline prenatal studies in the rat and rabbit that do not indicate increased susceptibility. Therefore, the contribution to the weight of evidence from the unacceptable mouse and rabbit studies indicating increased susceptibility is marginal.

Brain Cholinergic Receptors

Regarding potential prenatal toxicity, Eriksson and Nordberg (1990) orally administered deltamethrin at 0.1 and 1.2 mg/kg/d to 10 PND10 NMRI mice from 3 litters for 7 days in 20% fat emulsion. Mice receiving 1.2 mg/kg/d developed choreoathetosis following administration on days 10 to 13, and there was a decrease (7%) in muscarinic cholinergic receptors (MAChR) in the hippocampus and increase (10%) in the nicotinic receptors in the cerebral cortex 24 hours following the last dose. The 0.7 mg/kg/d dose did not cause any clinical symptoms but increased

the muscarinic (8%) and nicotinic (21%) receptor density in the cortex. As a follow-up, ten-day old males received gavage administrations of 0.7 mg/kg of deltamethrin (>97%) prepared in a 20% fat emulsion once daily from postnatal days 10 to 16. Behavioral tests were conducted at 17 days and 4 months of age, and MAChR assays were performed at 4 months. No clinical signs of toxicity were seen; however, there were significant changes in locomotion, rearing, and activity variables for the 4-month old mice. No significant behavioral changes were observed in the 17-day old mice. MAChR assays on the 4-month old mice revealed a "tendency toward a decrease" ($p<0.05$) in the amount of specific tritium labeled quinuclidinyl-benzilate, [^{3}H]QNB binding sites in the cerebral cortex." No significant changes were reported for other brain regions (hippocampus and striatum). The study authors concluded that deltamethrin "affects the cholinergic system during its rapid development, leading to permanent changes in the animals as adults" (Eriksson and Fredriksson 1991).

In a similar study using the same design, deltamethrin was administered to 10-day old NMRI mice in egg lecithin and peanut oil (1:10, w:w) or corn oil at 0.7 mg/kg/day for 7 consecutive days. No clinical signs of intoxication were noted in any of the mice. In the egg lecithin:peanut oil vehicle mice, at 4 months, activity was increased and habituation was decreased. Muscarinic receptor density in the cortex was not measured. With the corn oil vehicle, in 17 day old mice, approximately 24 hours after the last deltamethrin dose, there was no effect on behavior but there was an increase in receptor density. At 4 months, one experiment resulted in decreased habituation with no effect on muscarinic receptor density, and a second resulted in no behavioral effects but a decrease in muscarinic receptor density (unpublished data, Muhammad and Ray, 1997).

While these studies (Eriksson and Nordberg 1990; Eriksson and Fredriksson 1991; Muhammad and Ray, 1997) contribute to the general knowledge of deltamethrin toxicity, there are key factors which preclude them from supporting retention of the 10X FQPA factor. Three studies used the same experimental design; daily dosing of deltamethrin to 10-day old mice for seven consecutive days followed by evaluation of motor activity, nicotinic, and muscarinic receptor density. However, there was a lack of consistency in the responses for the measured endpoints. Furthermore, Shafer et al. (2005) indicates that [^{3}H]QNB binding assay, the technique used to measure muscarinic receptor density, may not be a robust response to developmental exposure of pyrethroids based on variability across several laboratories. Furthermore, the use of multiple pups from the same litter without statistical correction inflates the sample size and increases the probability of a type I statistical error.

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Appendix III. Data Call-In for Immunotoxicity Study

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.
Practical Utility of the Data
How will the data be used? These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

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R175290

Chemical Name: ***Deltamethrin***

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HED File Code: 13000 Tox Reviews
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